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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,659	07/20/2000	Tommy Abrahamsson	1103326 0629	9094

7590 08/27/2004

White & Case
Patent Department
1155 Avenue of the Americas
New York, NY 10036-2787

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/600,659	ABRAHAMSSON ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 August 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *11 August 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached sheets*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *6 and 7*.

Claim(s) rejected: *2,4,5,8,41 and 42*.

Claim(s) withdrawn from consideration: *3,9,11-17,19-23,25,26,28-33,47,54 and 61*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Advisory Action

The response filed 8/11/04 directs an amendment of claim 2. Claims 2-9, 11-17, 19-23, 25, 26, 28-33, 41, 42, 47, 54, 61 remain pending, of which claims 3, 9, 11-17, 19-23, 25, 26, 28-33, 47, 54, 61 remain withdrawn from consideration. Claims 2, 4-8, 41, 42 are active with respect to this Office action.

As indicated previously, the abbreviation "**CPU**" hereinbelow refers to carboxypeptidase U.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over

Eisenbach-Schwartz (USP 6,126,939) in view of Watson (USP 6,326,386)

As indicated previously, Eisenbach-Schwartz discloses (col 3, line 37) that the dipeptide Arg-Cys can be used to treat various inflammatory disorders, such as those recited in cols 5-6 of the reference. This compound is encompassed by formula I of claim 2 when the substituent variables correspond as follows:

R1 = C_4-alkyl substituted with two basic groups
X = -CO-NH-
Y = $-CH_2-$
R2 = hydrogen
R3 = -COOH
R4 = -SH

Applicants have argued that the amendment to claim 2 is effective to exclude the dipeptide Arg-Cys. However, this is not true. Claim 2 still permits substituent variable R^2 to be C_4-alkyl that is substituted with two basic groups (e.g., amino and guanidine). It is noted also that the possibility of "X" being -NH-CO- has been eliminated; at the same time, however, "X" can still be –CO-NH-. However, reciting (in the claim) that "X" can be –CO-NH- generates some degree of ambiguity, since the "polarity" of the amide bond is not clearly specified. When the claim permitted "X" to be **either** -NH-CO- **or** -CO-NH- , there was no ambiguity, since both of the following were clearly encompassed (for the case of variable R^6 representing a hydrogen atom):

$$R^1\text{-}\mathbf{CO\text{-}NH}\text{-}C(R^2)(R^3)\text{-}Y\text{-}R^4$$

R^1-**NH-CO**-C(R^2)(R^3)-Y-R^4

But if **either** of the two possibilities for "X" is eliminated, it becomes unclear what the "polarity" of "X" can be (or must be). Notwithstanding the ambiguity, the examiner would argue that of the two options above (for polarity of the amide bond), the first of the two options is the more likely interpretation of what is permitted by claim 2 in accordance with the amendment filed 8/11/04. Thus, whether the first of the two possibilities applies, or whether the claim is merely ambiguous, either way claim 2 still encompasses the dipeptide in question.

The rejection is maintained.

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Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over Ondetti (USP 4,177,277) in view of Watson (USP 6,326,386).

As indicated previously, Ondetti discloses (col 3, line 18+) compounds that are useful to treat cardiovascular conditions and inflammatory conditions. The compounds can also be used (col 7, line 57) to treat oedema. At the time of the final Office action, the following compound was encompassed by instant claim 2 as well as the prior art genus (applicants' variables are used hereinbelow):

R1 = aminopropyl
Y = $-CH_2-$
R2 = hydrogen
R3 = -COOH

R4 = -SH

It is true that the amendment filed 8/11/04 would exclude the possibility of R^1 being aminopropyl. However, claim 2 (as amended) does not exclude aminobutyl. While the possibility of variable "m" (of Ondetti) representing the integer 5 is not stated in the reference, the medicinal chemist of ordinary skill would have regarded a compound containing aminobutyl to be an "obvious variant" of an otherwise identical compound containing aminopropyl. That is, the two compounds in question are close homologs differing only in the presence of one methylene group. The medicinal chemist of ordinary skill would have expected, *a priori*, substantially identical activity for the two homologs. [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)].

The rejection is maintained.

✧

Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. '103 as being unpatentable over Eisenbach-Schwartz (USP 6,126,939) in view of Franson (USP 6,020,510).

The disclosures of the references were indicated previously. Applicants have argued that the amendment to claim 2 is effective to exclude the dipeptide Arg-Cys. As indicated above, this dipeptide is still encompassed by the claims.

The rejection is maintained.

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Applicants have also responded to the examiner's remarks in the final Office action concerning the extent to which the "unexpected results" (tables I, II and III, specification) may extend to other thrombin inhibitors which were never contemplated by applicants, or at least which were never disclosed in the specification. Applicants have argued that when thrombin is inhibited by argatroban, the clot lysis is enhanced due to decreased activation of CPU; Hashimoto (*Thrombosis and Haemostasis*, 2002, 87:110-113) is cited in support of this. Applicants have also stated that enhancement of clot lysis is observed when thrombin is inhibited by hirudin; Latacha (*Journal of Thrombosis and Haemostasis*, 2003, 128-134) is cited in support of this statement. The result to which applicants have referred (in Latacha) was conducted in the presence of plasminogen activators, and as such the issues are obscured by the presence of such. Latacha was not concerned with the issue of additive *versus* synergistic results for a combination of a thrombin inhibitor and a CPU inhibitor. Hashimoto also does not address this issue. The fact that "additive" results may be obtained for these two agents has been stipulated to by the examiner, and indeed forms the basis for the obviousness rejections. The references cited by applicants do not show "unexpected results" that are directly relevant to the issue raised by the examiner's §103 rejections.

Applicants have also responded to the following statement made by the examiner in the final Office action:

> Further, if the artisan of ordinary skill is intent on treating Alzheimer's Disease or atherosclerosis or septic shock (for example), he is unlikely to be concerned about the degree of inhibition of fibrin deposition in the lungs. Thus, for treatment of a disease in which fibrin deposition in the lung does not occur, the results presented (tables I – III, specification) are not especially "unexpected".

In response to this, applicants have argued that they are only claiming treatment of thrombosis and hypercoagulability. However, applicants are claiming neither. What is claimed is a composition, not any method of use. The examiner's argument could stop there and be sufficient. In addition, however, it is noted (and was noted previously) that on page 33 of the instant specification, it is asserted that various diseases can be successfully treated with CPU inhibitors. Such diseases include, e.g., Alzheimer's, atherosclerosis and septic shock. Thus, the claims are drawn to compositions, and as such, all uses are encompassed. In addition, however, various uses are suggested which have little relevance to the "unexpected results" that were obtained.

Applicants have also argued that claims 6 and 7 are in condition for allowance. However, these claims are objected to because of their dependence on rejected claims.

✷

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton 8/19/04

Jon P. Weber, Ph.D.
Primary Examiner